Models of antibody responses during HIV infection

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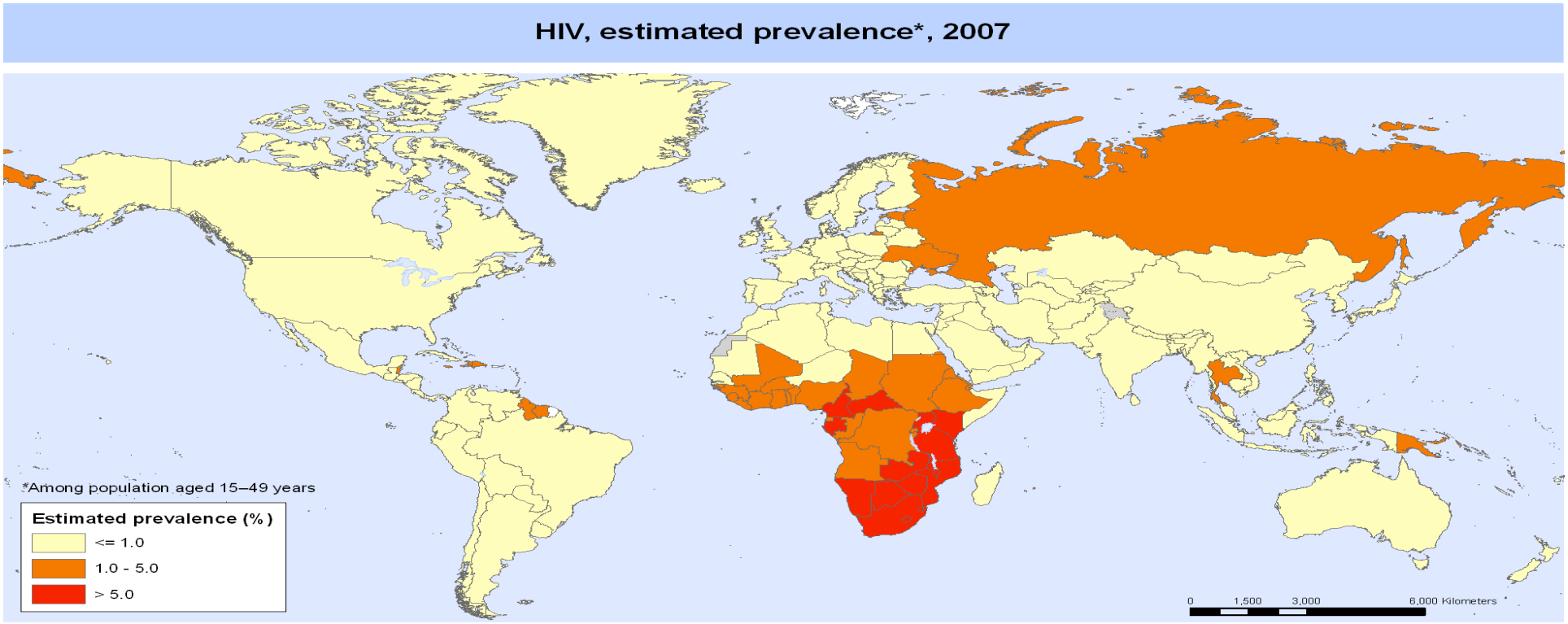

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Data Source: WHO/UNAIDS
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

- 22 million people have died of AIDS
- 33 million people living with HIV/AIDS
- 14,000 new infections every day

20 years of research

- HIV-specific antibody test developed for blood screening
- Detection of neutralizing antibodies against HIV

1980s

- Primary HIV isolates are highly resistant to neutralization
- Viruses rapidly escape neutralizing antibodies in vivo
- Most V3 loop antibodies are strain-specific (few exceptions)
- CD4-binding site antibodies are abundant but do not neutralize primary HIV-1 isolates (few exceptions)
- Majority of envelope-specific antibodies are non-neutralizing and do not recognize native envelope trimer
- Broadly neutralizing antibodies IgG1b12, 2F5, 2G12 identified

1990s

- Interference with CD4 and coreceptor binding is main mechanism of neutralizing antibodies against gp120
- Structure–function analysis of gp120 confirms modes of antibody interaction

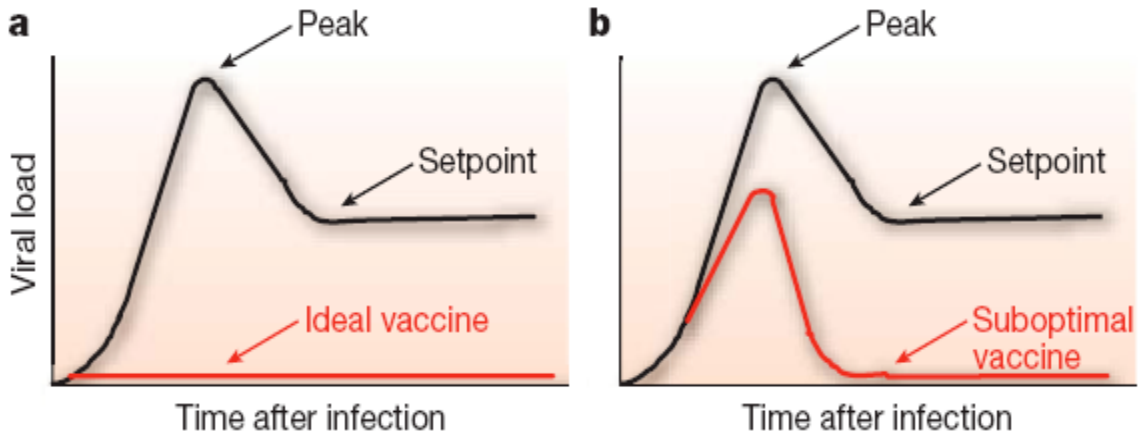
- Importance of MPER in gp41 -- broadly neutralizing MAbs 4E10 and Z13
- Broadly neutralizing MAbs Ig1B12, 2G12, 2F5, 4E10 have characteristic structural features
- Passive immunization studies -- vivo evidence of neutralization activity of broadly neutralizing MAbs
- Virus escape to antibody neutralization occurs already in acute infection.
- Selection in viral transmission and limit in superinfection

2000s

M Huber, J Int Med 07

Goal of HIV vaccine

- To prevent infection
- To reduce viral loads and clinical disease progression after infection



Vaccine trials to date

- AIDSVax
  - Rocombinant gp120 protein as vaccine vector
  - Induced strain-specific Ab but failed to induce broadly neutralizing Ab
- STEP
  - Induction of cellular mediated immune responses
  - Recombinant adenovirus serotype 5
  - Suppressed by pre-existing AD5-specific Ab
  - Enhanced HIV infection
- RV 144
  - ALVAC-HIV recombinant canarypox + AIDSVax
  - Successful in reducing infectivity rates
  - Believed inefficient for clade C

What are the challenges?

Virus

- Extensive viral clade and sequence diversity
- Early establishment of latent viral reservoirs
- Viral evasion of humoral and cellular immune responses

Antibody

- Responses are strain-specific (ssAb)
- No method exists to elicit broadly reactive neutralizing antibodies
  - Deleted during selection
  - Wrong conformation
  - Outcompeted

Depletion of interfering antibodies in chronic hepatitis C patients and vaccinated chimpanzees reveals broad cross-genotype neutralizing activity

P Zhanga, L Zhonga, EB Strublea, HW, A Kachkob, K Mihalikb, ML Virata-Theimera, HJ Alterc, S Feinstoneb, M Majorb,
PNAS, 2009 (105).

Why do adaptive immune responses cross-react?

Karen J. Fairlie-Clarke, David M. Shuker and Andrea L. Graham
Evolutionary Applications 2009 (2).

Competition

Hypothesis

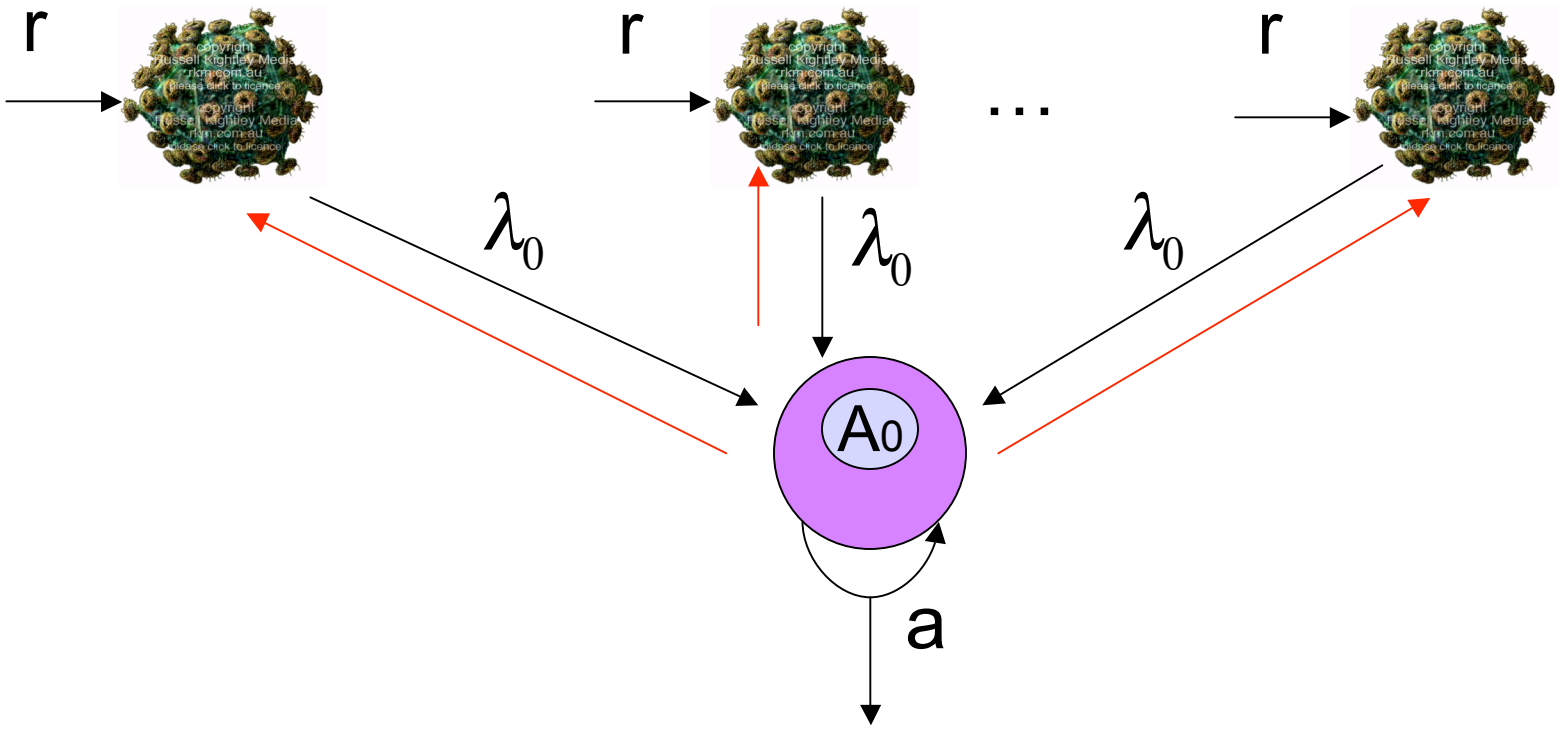
- Presence of strain-specific antibodies doesn't have to exclude the presence of broadly neutralizing ones
- Antibodies can compete with each other for
  - antigen
  - space in the lymph nodes
  - T cell conjugates and/or kinetic prolongation

Model

- Competition between the two antibody types.
- Find the parameter region where bnAb is made inefficient by ssAb

Model without competition

-continuous immunization



Model without competition

-continuous immunization

Consider n strain of virus V_i, and one broadly neutralizing antibody A_0.

$$\frac{dV_i}{dt} = (r - K_0 A_0)V_i$$
$$\frac{dA_0}{dt} = \lambda_0 \sum_{i=1}^{n} V_i + A_0(a - \beta A_0)$$

where $V_i(t_i) = V_0,\ A_i(t_i) = 0,\ A_0(0) = 0.$

Steady-state analysis

1. The no-infection steady state $E_0 = (0, 0,...,0,0)$ is always unstable.

2. The disease free steady state $E_1 = (0, 0,...,0, a/\beta)$ is GAS when $r < K_0 \frac{a}{\beta}$.

3. The chronic steady state $E^* = (V_1^*, V_2^*, ..., V_n^*, A_0^*)$.

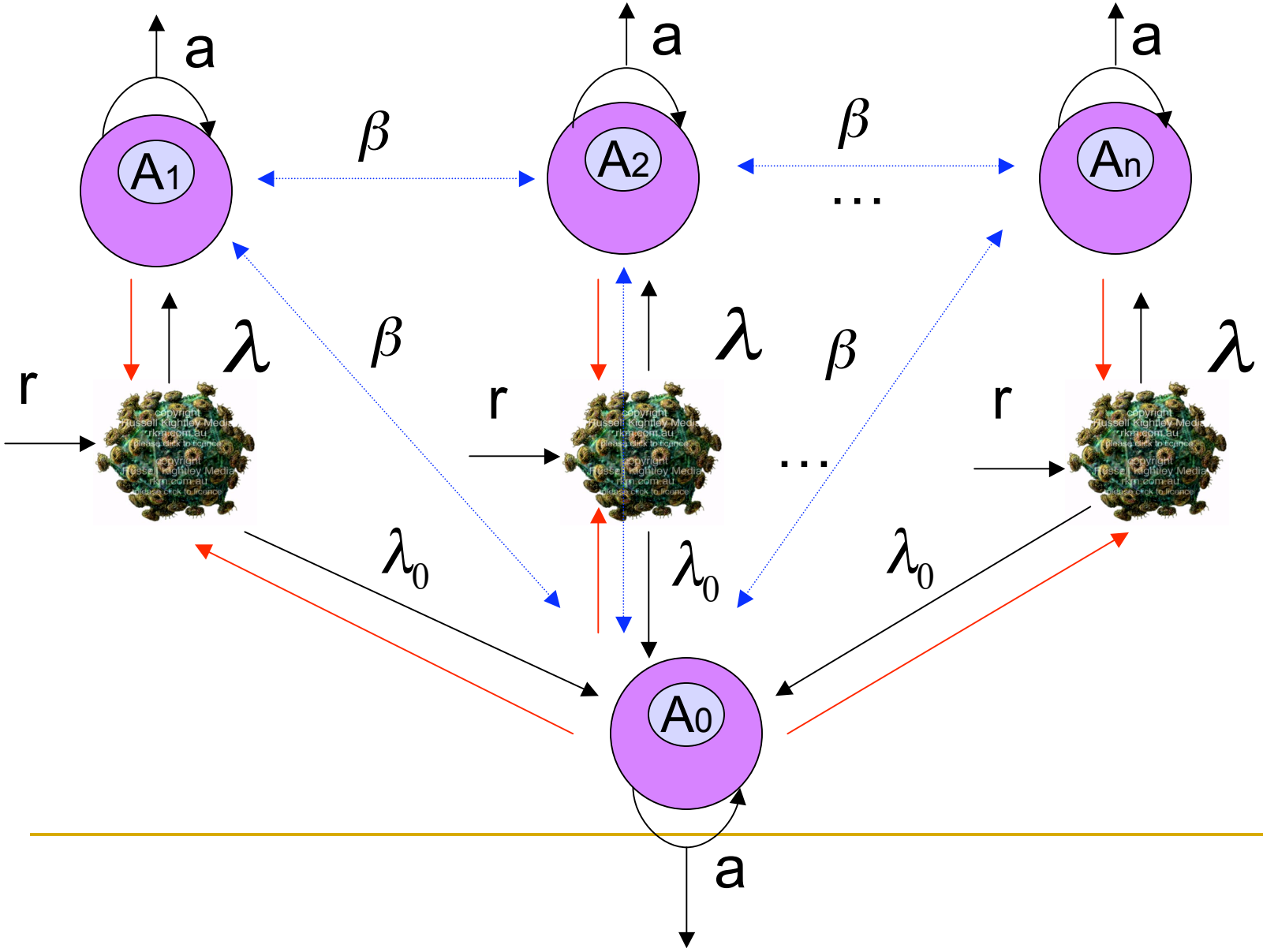
$$E^* = \{(V_1^*, V_2^*, ...V_n^*, A_0^*) / V_i \geq 0,\ A_0 > 0,\ V_T = A_0^* (\beta A_0^* - a),\ A_0^* = r/K_0\}.$$

is GAS when $r > K_0 \frac{a}{\beta}$.

Biological interpretation: When the virus replication rate is smaller then the product between the bnAb affinity rate and the antibody life span viruses will be cleared, otherwise some persist.

Model with competition

-continuous immunization



Antibody competition model

Consider n strain of virus V_i, n strain specific antibodies A_i and one broadly neutralizing antibody A_0.

$$\frac{dV_i}{dt} = (r - KA_i - K_0 A_0)V_i$$
$$\frac{dA_i}{dt} = \lambda V_i + A_i(a - \beta A_T)$$
$$\frac{dA_0}{dt} = \lambda_0 \sum_{i=1}^{n} V_i + A_0(a - \beta A_T)$$

where $A_T = A_0 + \sum_{i=1}^{n} A_i$, $V_i(t_i) = V_0$, $A_i(t_i) = 0$, $A_0(0) = 0$.

Steady-state analysis

1. The no-infection steady state $S_0 = (0, 0, 0)$.

2. The disease free steady states

$$S_1 = \{(0, A^*, A_0^*)/A_i \geq 0, A_0 \geq 0, \ A_T = a/\beta\} \ .$$

3. Let $\varnothing \neq I \subset \{1, 2, ..., n\}$ with $\#(I) = m \geq 1$. Then there exist steady states (V^*, A^*, A_0^*) with $A_j^* , V_j^* > 0$, for all $j \in I$ and $A_j^* = V_j^* = 0$ for all $j \notin I$ iff

$$r > \frac{m\lambda_0 K_0 + \lambda K}{m(\lambda + \lambda_0)} \frac{a}{\beta}.$$

Moreover, the non-zero components of the steady state are

$$A_j^* = \frac{\lambda}{m \ \lambda_0} A_0^*, A_0^* = \frac{m}{m + \frac{\lambda K}{\lambda_0 K_0}} \frac{r}{K_0},$$

$$V_j^* = \frac{\beta}{m\lambda_0} \left((1 + \frac{\lambda}{\lambda_0}) A_0^* - \frac{a}{\beta}\right) A_0^*.$$

Observations

1. There is a unique chronic steady state when $m = n$ which is GAS when

$$r > \frac{n\lambda_0 K_0 + \lambda K}{n(\lambda + \lambda_0)} \frac{a}{\beta}.$$

2. If $r > \frac{\lambda_0 K_0 + \lambda K}{\lambda + \lambda_0} \frac{a}{\beta}$ then $r > \frac{m\lambda_0 K_0 + \lambda K}{m(\lambda + \lambda_0)} \frac{a}{\beta}$ for all $m \geq 1$.

3. If $r < \frac{n\lambda_0 K_0 + \lambda K}{n(\lambda + \lambda_0)} \frac{a}{\beta}$, then $r < \frac{m\lambda_0 K_0 + \lambda K}{m(\lambda + \lambda_0)} \frac{a}{\beta}$ for all $m \leq n$ and all virus strains will be cleared.

Biological interpretation: When the combined effect of the bnAb and ssAb exceeds the virus replication rate viruses are cleared, otherwise some persist.

Global stability results

Theorem. When m=n and $r > \frac{a}{\beta}\frac{nK_0\lambda_0 + K\lambda}{n(\lambda+\lambda_0)}$ the chronic steady state is GAS.

Proof :

$$W(V_1,V_2,\ldots,V_n,A_0) = \sum_{i=1}^{n} V_i^* \int_{V_i^*}^{V_i} \left(\frac{1}{V_i^*} - \frac{1}{\tau}\right) d\tau + \frac{1}{\lambda_0}\int_{A_0^*}^{A_0} (K_0\tau - K_0 A_0^*) d\tau + \frac{1}{\lambda}\sum_{i=1}^{n}\int_{A_i^*}^{A_i} (K_0\tau - K_0 A_i^*) d\tau$$

g$W(V_1,V_2,\ldots,V_n,A_1,\ldots,A_n,A_0) \geq 0$ for all $(V_1,V_2,\ldots,V_n,A_1,\ldots,A_n,A_0)$.

g$W(V_1,V_2,\ldots,V_n,A_1,\ldots,A_n,A_0) = 0$ for $(V_1,V_2,\ldots,V_n,A_1,\ldots,A_n,A_0) = (V_1^*,V_2^*,\ldots,V_n^*,A_1^*,\ldots,A_n^*,A_0^*)$.

g$\dot{W}(V_1,V_2,\ldots,V_n,A_1,\ldots,A_n,A_0) \leq 0$ for all $(V_1,V_2,\ldots,V_n,A_1,\ldots,A_n,A_0)$.

$\{(V_1^*,V_2^*,\ldots,V_n^*,A_1^*,\ldots,A_n^*,A_0^*)\}$ is the largest invariant subset of $\{\dot{W} = 0\}$.

Then, from the LaSalle Invariance Principle, all solutions converge to S^*.

Global stability results

Lemma 4. Assume that $m = n$ and $r < \frac{a}{\beta}\frac{nK_0\lambda_0 + K\lambda}{n(\lambda + \lambda_0)}$. Then there are only trivial steady states ($V_i^* = 0$ for all i). Then all solutions converge to the set of steady states given by $A_T = a / \beta$.

Biological interpretation: When the combined effect of strain specific and broadly neutralizing antibody exceeds the virus replication rate, the virus is cleared, otherwise it persists.

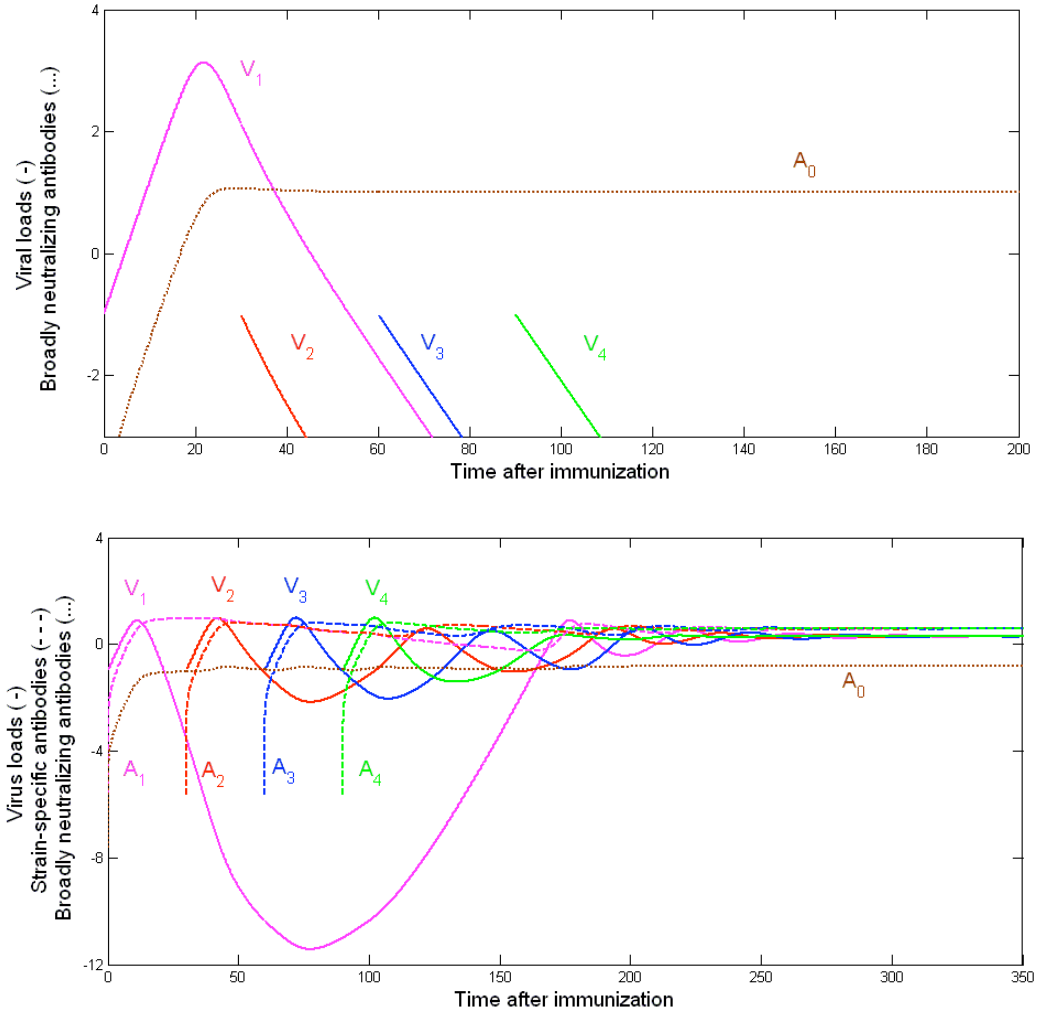
Model prediction

For parameters

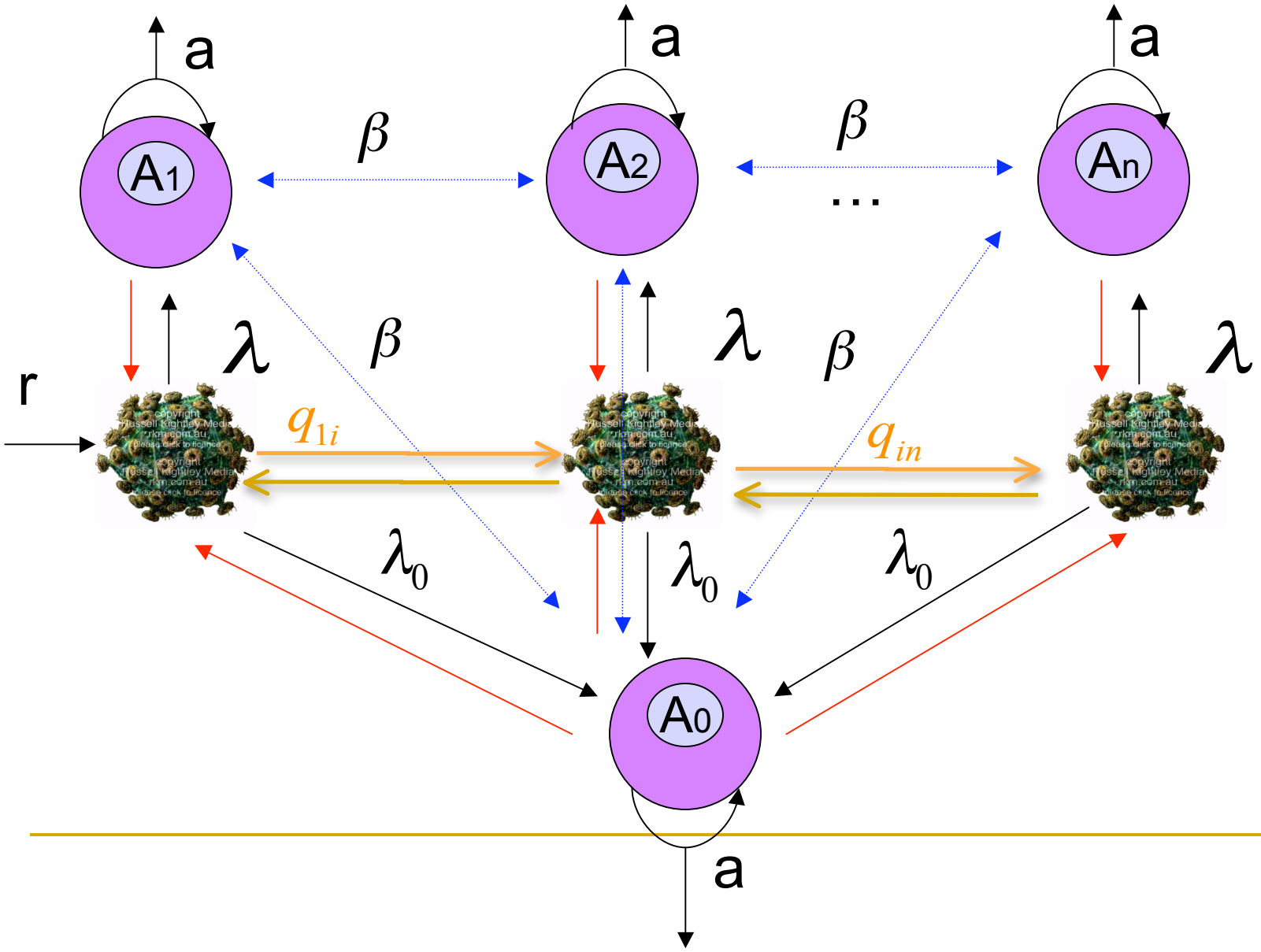
$$\frac{a}{\beta}\frac{nK_0\lambda_0 + K\lambda}{n(\lambda + \lambda_0)} < r < K_0\frac{a}{\beta}$$

- Virus gets cleared when there is no competition between antibodies.
- Virus reaches a steady state when there is competition between SS and BN Ab.

Numerical results



Natural infection - mutations



Mutation model

Start with virus V_1 and responses A_1 and A_0, such that

$$V_1(0) = V_{1,0} \text{ and } V_j(0) = A_j(0) = A_0(0) = A_1(0) = 0.$$

$$\frac{dV_i}{dt} = r\sum_{j=1}^{n} q_{ij}V_j - (KA_i + K_0A_0)V_i$$

$$\frac{dA_i}{dt} = \lambda V_i + A_i(a - \beta A_T)$$

$$\frac{dA_0}{dt} = \lambda_0 \sum_{i=1}^{n} V_i + A_0(a - \beta A_T)$$

where $Q = \{q_{ij}\}_{i,j}$ is the mutation matrix: $0 \le q_{ij} \le 1$

$$\sum_{i=1}^{n} q_{ij} = 1, \text{ for all } 1 \le j \le n.$$

No competition

Let $V = (V_1, V_2, ..., V_n)$ interact with A_0.

The dynamics of the systems (1) and (2) are quivalent

(1)
$$\frac{dV}{dt} = (rQ - K_0 A_0 I_n)V$$
$$\frac{dA_0}{dt} = \lambda_0 V_T + A_0(a - \beta A_0)$$

(2)
$$\frac{dV_T}{dt} = (r - K_0 A_0)V_T$$
$$\frac{dA_0}{dt} = \lambda_0 V_T + A_0(a - \beta A_0)$$

when the dominant eigenvalue of Q=$\{q_{ij}\}$ is simple, with corresponding eigenvector $z \geq 0$ s.t. $Qz = z$.

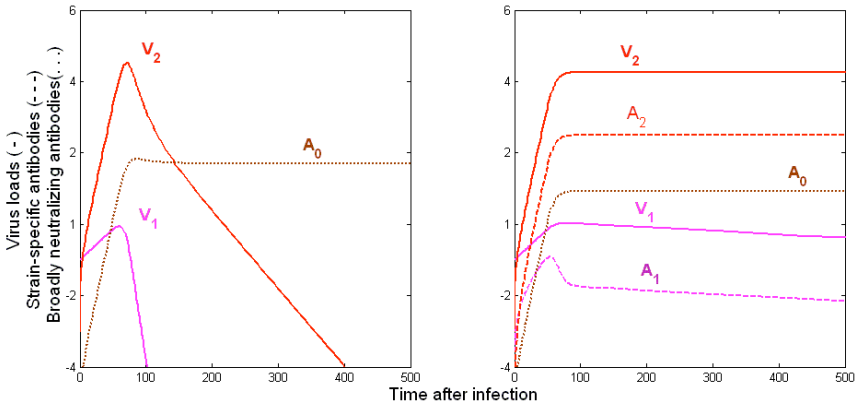
For example

1. Q is irreducible. Then z is an entry wise positive vector by Perron Frobenius Theorem.

When $r<K_0 \frac{a}{\beta}$ all virus strains are cleared.

When $r>K_0 \frac{a}{\beta}$ all virus strains persists.

2. $$Q = \begin{pmatrix} 1-q_{12} & 0 & 0 & \dots & 0 & 0 \\ q_{12} & 1-q_{23} & 0 & \dots & 0 & 0 \\ \dots & & & & & \\ 0 & 0 & 0 & & q_{n-1n} & 1 \end{pmatrix}.$$



When $r<K_0 \frac{a}{\beta}$ all virus strains are cleared.

When $r>K_0 \frac{a}{\beta}$ only V_n persists.

Competition

For $n = 2$,

$$q_{11} = 1 - \alpha;\ q_{12} = q_{21} = \alpha;\ q_{22} = 1,$$

The viruses are cleared when

$$r < \Omega\ K_0 \frac{a}{\beta}$$

and persist when

$$r > \Omega K_0\ \frac{a}{\beta},$$

$$\Omega = \frac{\frac{K}{K_0}\left(\frac{\lambda}{\lambda_0} + \frac{K_0}{K}\right)\left(\frac{\lambda}{\lambda_0} + 2\frac{K_0}{K}\right)}{\left(1 + \frac{\lambda}{\lambda_0}\right)\left\{\left(3\frac{\lambda}{\lambda_0} + 4\frac{K_0}{K}\right) - \alpha\left(2\frac{\lambda}{\lambda_0} + 4\frac{K_0}{K}\right) + \sqrt{\left(\left(3\frac{\lambda}{\lambda_0} + 4\frac{K_0}{K}\right) - \alpha\left(2\frac{\lambda}{\lambda_0} + 4\frac{K_0}{K}\right)\right)^2 - 8\left(\frac{\lambda}{\lambda_0} + \frac{K_0}{K}\right)\left(\frac{\lambda}{\lambda_0} + 2\frac{K_0}{K}\right)(1-\alpha)^2}\right\}}$$

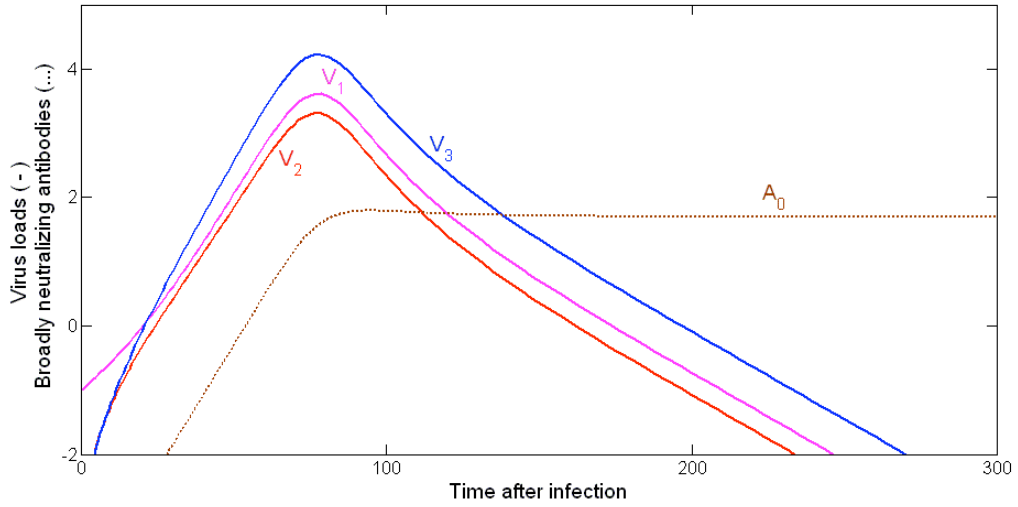
Model prediction

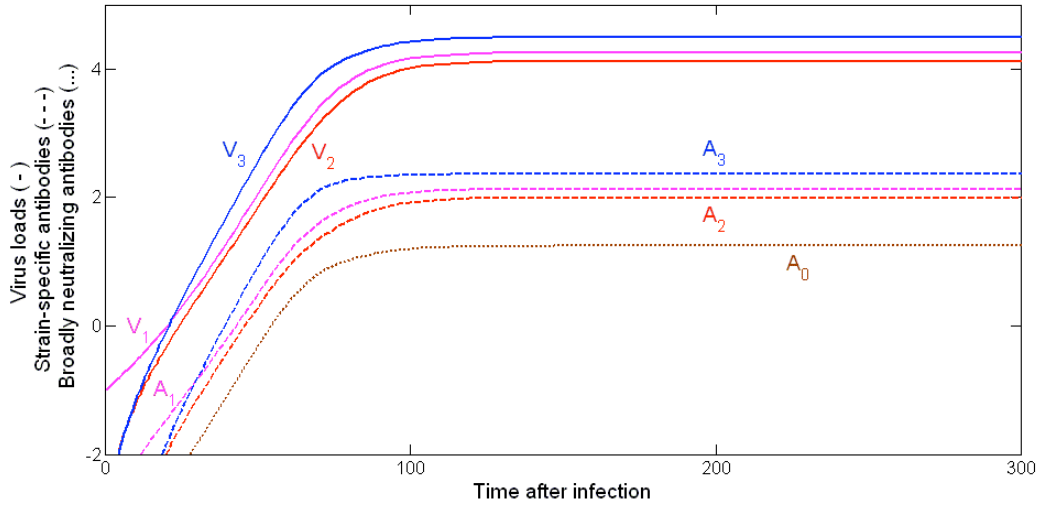
For parameters

$$\Omega K_0 \frac{a}{\beta} < r < K_0 \frac{a}{\beta}$$

- Virus gets cleared when there is no competition between antibodies.
- Virus reaches a steady state when there is competition between SS and BN Ab.

Numerical results for n strains





Conclusions and future work

- Broadly neutralizing antibodies alone can control multiple HIV infections.
- Additional immune events directed against specific HIV viral strains weaken the immune system defense, by limiting the growth of B cells producing broadly neutralizing antibodies.
- Under global resource limitation, HIV will be controlled only when there is no delay in a viral-specific antibody response. We know that this is not achieved in vivo.
- Competition between HIV-strain specific and analogous antibodies might explain the immune response's ineffectiveness in controlling long term HIV infections.

Conclusions and future work

- Use in a vaccine trial:

  -increase the affinity of bnAB (K_0)

  -increase the antibody levels (λ_0)

  -decrease n

- Biological validation.